ME/CFS, MCAS, and PTSD Research Summary

Integrated Gene–Environment Model of Immune-Metabolic-Neuroinflammatory Dysregulation, Mast-Cell Reactivity, Lactate Dysfunction, Glymphatic Impairment, Sensory Neuropathy, Environmental Sensitivity, and PTSD-Like Autonomic Symptoms

Updated Integrated Version August 3, 2026

Introductory Note on the Newly Integrated Research

This updated version rewrites the full working hypothesis by merging the prior ME/CFS, MCAS, and PTSD research summary with the newer insertable material and by including related author names and publication dates where they were available. The added research strengthens several major parts of the model: chronic glucocorticoid exposure and impaired MCT1-mediated lactate transport; oxidative stress, NLRP3 inflammasome activation, and kynurenine-pathway dysregulation; cytokine-driven PTSD mechanisms; lactate-mediated antiviral suppression and NF-κB amplification; AhR-related mast-cell and environmental-stressor pathways; particulate pollution, diesel exhaust, and sensory hyper-reactivity; weather and air-quality sensitivity in ME/CFS; HIF-1α–PKM2–PDK4 metabolic locking; mast-cell–HIF-1α amplification; Substance P–MrgprX2 neuroimmune mast-cell activation; IL-1β-encoding stress neurons; reciprocal glycolysis–NLRP3 activation; intestinal barrier restoration; protein lactylation in PTSD, cardiovascular disease, and CFS-like models; probiotic effects on metabolic stress and lactate-related genes; persistent cytolytic CD8+ T-cell activity in long COVID; altered T-cell metabolism in ME/CFS; and heterogeneous circulating miRNA changes converging on SIRT1 and related metabolic targets.

Several specific studies now anchor the model more clearly. Kita-Shirakura et al. (2026) support the idea that chronic glucocorticoid exposure can reduce cerebrovascular MCT1 function, elevate hippocampal lactate, suppress hippocampal neurogenesis, and contribute to behavioral abnormalities. Bahaa et al. (2026) support the clustering of oxidative stress, NLRP3 inflammasome activation, and kynurenine-pathway dysregulation in neuropsychiatric inflammatory states. Ogłodek (2026) supports the framing of pro-inflammatory cytokine processing as a central mechanism in PTSD pathophysiology. Tian et al. (2026) add a major lactate-immunity mechanism by showing that host-derived lactic acid can impair interferon

efficacy while amplifying NF-κB-driven inflammation. Zhou et al. (2013), Vogel et al. (2020), Cheng et al. (2024), Jin et al. (2019), Hidaka et al. (2017), and Jones et al. (2024) strengthen the environmental-sensitivity portion of the model through AhR signaling, mast-cell activation, pollutant effects, particulate exposure, sensory hyper-reactivity, pain, and fatigue.

Other added studies extend the model into immune metabolism, gut-brain signaling, lactylation, and post-viral immune persistence. Hashimoto et al. (2026) identify central IL-1β-responsive neurons that can drive systemic inflammatory and autonomic responses, providing a neural bridge between stress and inflammation. Miller and Johnson (2026) support the importance of dietary amino acids and intestinal barrier restoration. Kozlakidis et al. (2023) support protein lactylation as an emerging link between lactate, epigenetic regulation, PTSD, cardiovascular disease, and inflammatory aging. Sun et al. (2025) provide direct CFS-model evidence for a PKM2–lactate–H4K12 lactylation–NF-κB pathway driving neuroinflammation and mitochondrial damage. Song et al. (2026) support a gut-metabolic-lactate node through probiotic effects on fatigue, inflammation, pain sensitivity, Hcar1, and Slc16a1/MCT1. Ma et al. (2026) support persistent cytolytic CD8+ T-cell activity in long COVID involving SARS-CoV-2 and herpesvirus epitopes. Mandarano et al. (2020) support altered T-cell metabolism in ME/CFS. Kaczmarek (2023) supports the idea that heterogeneous circulating miRNA changes in ME/CFS may converge on shared target-gene clusters including SIRT1, mitochondrial dynamics, antioxidant defenses, hypoxia adaptation, and circadian regulation.

These additions do not convert the hypothesis into a formal diagnosis. They are included as research-informed mechanisms to support clinical discussion and further evaluation. The model remains provisional. Its purpose is to organize plausible pathways that may connect ME/CFS, MCAS-like reactivity, PTSD-like autonomic symptoms, sensory neuropathy/hypoesthesia, chemical and environmental sensitivity, lactate abnormalities, glymphatic impairment, gut-brain-immune signaling, and abrupt multi-system flares.

Purpose and Overall Framing

This is a working research summary, not a formal diagnosis. It synthesizes personal clinical observations, genetic data, environmental exposure history, real-time biomarker tracking, family history, symptom patterns, and biomedical literature into a unified explanatory model. The goal is to organize plausible interconnected pathways that may explain the fused pattern of ME/CFS, MCAS-like reactivity, PTSD-like autonomic and fear symptoms, neurological instability, sensory neuropathy/hypoesthesia, sleep disruption, gut sensitivity, chemical sensitivity, environmental intolerance, lactate changes, and abrupt multi-system flares.

The central idea is that these symptoms may not represent separate, unrelated problems. Instead, they may be different outputs of one unstable immune-metabolic-neuroendocrine-neuroinflammatory network shaped by gene–environment interactions, early toxicant exposure, viral or infectious priming, impaired glucocorticoid signaling, mast-cell activation, histamine intolerance, altered lactate handling, astrocyte dysfunction, glymphatic impairment, microglial activation, circadian disruption, gut-barrier

dysfunction, altered T-cell metabolism, miRNA-mediated regulation, and a lowered physiological stress threshold.

The most clinically useful framing is that the system may be operating with a lowered physiological stress threshold. When below threshold, symptoms may still be present but relatively more manageable. When stressors accumulate, such as poor sleep, physical exertion, cognitive load, emotional stress, infection, chemical exposure, air pollution, smoke, mold, pesticides, construction dust, food triggers, gut irritation, dehydration, orthostatic stress, sensory overload, poor water quality, or medical procedures, the system may abruptly cross a tipping point. Once that threshold is crossed, multiple loops may activate at once, producing a flare that includes PEM, mast-cell symptoms, histamine reactions, autonomic instability, lactate elevation, sensory overload, neurological symptoms, sleep disruption, and sudden fear or alarm states.

Background: The Overlapping Conditions

ME/CFS is a chronic multi-system illness characterized by profound fatigue, unrefreshing sleep, cognitive impairment, orthostatic intolerance, and post-exertional malaise. In this case, the ME/CFS pattern includes sudden crashes, severe fatigue, brain fog, sensory overload, photophobia, orthostatic symptoms, sleep disruption, cognitive slowing, and a markedly lowered threshold for relapse. PEM is central because physical, cognitive, emotional, sensory, infectious, chemical, orthostatic, or procedural stress can trigger delayed and prolonged worsening. This worsening is not ordinary tiredness. It can feel like a whole-body immune-metabolic crash involving neurological, autonomic, inflammatory, sensory, and metabolic symptoms at the same time.

MCAS-like symptoms include histamine-driven burning of the face and neck, flushing, heart-rate spikes with food or spices, vinegar sensitivity, smoke and chemical intolerance, air-pollution sensitivity, gut-triggered flares, migraines, sensory sensitivity, stress-triggered reactions, hives, itching, and likely nocturnal or early-morning symptom amplification. In this model, mast-cell activation is not limited to allergy-like reactions. Mast-cell mediators may amplify TNF-α, IL-1β, IL-6, IL-11, IL-33, histamine, tryptase, prostaglandins, leukotrienes, chemokines, MMP-9, type-2 cytokines, and other mediators that can affect blood vessels, nerves, the gut, the brain, the blood-brain barrier, and the autonomic nervous system. This helps explain why MCAS-like symptoms may feed into PEM, orthostatic symptoms, brain fog, pain, sensory overload, and threat-circuit activation.

PTSD-like symptoms appear as abrupt, switch-like fear or autonomic episodes, hypervigilance, impaired fear extinction, sudden autonomic arousal, and neurological features such as ataxia-like “wobbles,” syncope or near-syncope, photophobia with visual trails, shivering, temperature dysregulation, amnesia, and altered states that can occur with minimal or no obvious trigger. In this model, these symptoms are not framed as purely psychological. They may reflect dysregulation of threat circuitry, inflammatory cytokines, arousal systems, orexin signaling, locus coeruleus-norepinephrine output, amygdala reactivity, dopamine prediction-error

signaling, NMDA/glutamate signaling, kynurenine metabolites, astrocyte energy support, microglial activation, AQP4 function, and glymphatic clearance.

These symptom clusters overlap through one shared immune-metabolic-neuroendocrine-neuroinflammatory network. A single trigger can produce PEM, mast-cell and histamine symptoms, autonomic instability, cognitive dysfunction, neurological instability, movement symptoms, sensory overload, and fear/autonomic episodes. This suggests that ME/CFS, MCAS-like reactivity, and PTSD-like symptoms may be different expressions of a common threshold-based network rather than completely separate processes.

Core Hypothesis

The core hypothesis is that early genetic vulnerability, environmental exposure, developmental stress, infection, impaired detoxification resilience, altered stress-response regulation, immune priming, mast-cell activation, and glial vulnerability created a lowered physiological threshold. Once that threshold became chronically lowered, self-reinforcing loops involving inflammation, mast cells, histamine, astrocytes, lactate, glutamate, microglia, orexin, norepinephrine, NMDA signaling, dopamine, serotonin-kynurenine balance, circadian rhythm, glymphatic clearance, AQP4 polarization, mitochondrial function, gut-brain signaling, T-cell metabolism, miRNA regulation, and myelin/nerve repair may have maintained the illness state.

The proposed pattern is that genetic susceptibility plus early environmental exposure plus developmental stress plus impaired NR3C1/glucocorticoid regulation plus impaired NRF2 antioxidant response plus SIRT1/PGC-1α/AMPK dysfunction plus mast-cell and histamine activation plus kynurenine pathway overdrive plus glymphatic impairment plus AQP4 dysregulation plus glycolytic reprogramming plus HIF-1α–PKM2–PDK4 activation plus lactate-driven NLRP3 activation plus astrocytic metabolic dysfunction plus impaired lactate and glutamate handling plus orexin instability plus noradrenergic dysregulation plus microglial activation plus dopamine prediction-error disruption plus NMDA/GRIN2A vulnerability plus possible LRRK2/GBA-related vulnerability plus lactylation-related signaling may lower the threshold for PEM, MCAS-like flares, fear episodes, neurological instability, sensory neuropathy symptoms, movement symptoms, metabolic decompensation, and severe crashes.

This model helps explain why flares may feel abrupt and automatic. A person may seem relatively stable and then suddenly enter a crash state when the system crosses a physiological threshold. The switch may not be a single-organ event. It may reflect simultaneous activation of mast cells, inflammatory cytokines, lactate accumulation, impaired interferon responses, glymphatic clearance failure, astrocyte metabolic strain, microglial activation, autonomic dysregulation, altered blood flow, gut-derived inflammatory signaling, and threat-circuit instability.

Developmental Priming and Gene–Environment Interaction

The developmental priming phase likely began with early childhood exposure to contaminated well water and environmental toxicants in Elkhart, Indiana, from approximately 1965 to 1981, including concern for TCE and other chemicals related to railroad dumping and local contamination. This exposure history may have interacted with secondhand smoke exposure, possible malnutrition, chronic stress, maternal or early-life inflammatory signaling, and genetic susceptibility. The important point is not that any single exposure alone explains the illness. Rather, the model proposes that multiple exposures and vulnerabilities converged during development, lowering immune, metabolic, detoxification, barrier, and neuroendocrine resilience.

Relevant vulnerabilities in this model include inflammatory variants such as TNF-α rs1800629 AA and IL-1β-related risk, immune-regulatory factors such as CTLA4, inflammasome-related risk such as NLRP3, sensory-channel vulnerabilities involving TRPM3/TRPM8, complement-related variants involving CFB/CFH, HLA-DQ2.5/DQ8, histamine metabolism vulnerabilities involving AOC1/DAO and HNMT, glutamatergic vulnerability involving GRIN2A rs9922678 AA, reduced CYP3A4/CYP3A5 detoxification capacity, and possible LRRK2 G2019S and GBA-related vulnerabilities if clinically relevant.

This combination may have produced long-term immune-metabolic priming through immunotoxicity, oxidative stress, altered detoxification resilience, epigenetic changes, and dysregulation of NR3C1, the glucocorticoid receptor gene. TNF-α variants and decreased detoxification capacity may have exacerbated the effects of early environmental exposures, including toxicants such as TCE and other chemicals, as well as later exposures such as smoke, air pollution, pesticides, mold, construction dust, and poor water quality.

The 1983 viral pneumonia with heavy secondhand smoke exposure during a stressful period appears to have been the major tipping point. In this model, the system was already primed by gene–environment interactions, and the infection plus smoke exposure plus stress may have exceeded the remaining resilience threshold. Instead of returning fully to baseline, the system may have shifted into a persistent post-infectious immune-metabolic state.

Environmental Stressors, AhR Signaling, and Barrier-Surface Reactivity

The newly merged material strengthens the environmental-sensitivity portion of the model by adding a detailed role for the aryl hydrocarbon receptor, or AhR. Vogel et al. (2020) describe AhR as a central cellular target of environmental stressors, including polycyclic aromatic hydrocarbons, persistent organic pollutants, and particulate matter associated with air pollution. When activated by certain pollutants, AhR can induce cytochrome P450 enzymes, generate reactive oxygen species, interact with NRF2 antioxidant pathways, and promote inflammatory responses in barrier tissues and immune cells.

In this model, AhR serves as a bridge between environmental exposure and immune-metabolic dysregulation. Early or ongoing exposure to air pollution, smoke, diesel exhaust, particulate

matter, chemical fumes, pesticides, mold-associated compounds, or contaminated water may not simply irritate tissues. These exposures may activate AhR-dependent transcriptional programs that increase oxidative stress, alter detoxification demands, affect mast-cell behavior, disturb barrier integrity, and amplify inflammatory tone.

Zhou et al. (2013) add an important mast-cell layer by showing that AhR is involved in mast-cell homeostasis. AhR signaling appears to influence mast-cell differentiation, survival, mitochondrial function, calcium signaling, mediator release, cytokine production, and the balance between deficiency and over-reactivity. In this model, unstable AhR tone could contribute to both abnormal mast-cell regulation and exaggerated degranulation. Reduced beneficial AhR ligand availability from gut dysbiosis, combined with excessive pollutant-related AhR activation at barrier surfaces, may create a dysregulated AhR state that worsens mast-cell instability, oxidative stress, and environmental sensitivity.

Several pollutant-related mechanisms further support this link. Cheng et al. (2024) showed that diesel exhaust particles can activate mast cells through the AhR/NF-κB pathway and induce IL-33 expression, with the IL-33/ST2 axis promoting mast-cell migration and type-2 cytokine release. Jin et al. (2019) demonstrated that PM2.5 enhances FcεRI-mediated mast-cell signaling, increasing Syk activation, downstream signaling, degranulation, and cytokine production. Hidaka et al. (2017) showed that AhR activation by air-pollutant ligands in keratinocytes can induce artemin, increasing sensory nerve hyper-reactivity, itch hypersensitivity, and inflammation. In this case, these mechanisms fit with smoke-triggered hives, itching, burning, chemical sensitivity, and pollutant-linked mast-cell symptoms.

Jones, Haskin, and Younger (2024) add empirical support for environmental sensitivity in ME/CFS by reporting associations between daily weather or air-quality variables and pain and fatigue severity in women with ME/CFS. In this model, environmental sensitivity is therefore not treated as incidental or purely subjective. It may reflect measurable interactions between pollution, barrier tissues, mast cells, oxidative stress, vascular tone, neuroinflammation, and energy metabolism.

Viral “Hit-and-Run” Priming, Persistent T-Cell Activity, and Post-Viral Inflammation

A major addition to the model is the idea that viral “hit-and-run” mechanisms may create persistent glial and immune changes even after the initial infection has resolved. This is relevant to the 1983 viral pneumonia and to later research on post-infectious syndromes. Viral proteins or viral immune signatures may trigger astrocyte and microglial activation, alter mitochondrial function, disrupt blood-brain barrier regulation, and initiate a long-lasting neuroimmune state even after the acute infection is no longer active.

This mechanism matters because it provides a plausible bridge between an acute infection and persistent ME/CFS-like illness. A viral insult may not need to remain continuously present in the same form to produce ongoing symptoms. Instead, it may leave behind a changed state in

immune cells, microglia, astrocytes, endothelial cells, mast cells, T cells, or neuronal networks. If this viral priming occurs in a person with LRRK2-related immune vulnerability, impaired NRF2 antioxidant defense, glucocorticoid dysregulation, mast-cell reactivity, and impaired lactate handling, the result may be a persistent inflammatory-metabolic loop.

Ma et al. (2026) add persistent cytolytic CD8+ T-cell activity as a possible post-viral driver. Their work in long COVID found persistent cytolytic CD8+ T-cell populations specific for SARS-CoV-2 and herpesvirus epitopes, including CMV and EBV. In this model, such persistent cytolytic immune activity may provide an upstream source of chronic tissue stress and low-grade inflammation. That inflammatory milieu may promote glucocorticoid receptor resistance, disrupt HPA-axis feedback, sustain cytokine signaling, and amplify metabolic, mast-cell, and neuroimmune loops.

Mandarano et al. (2020) support the idea of altered T-cell metabolism in ME/CFS. Their work showed that T cells from ME/CFS patients exhibit metabolic differences, including altered mitochondrial membrane potential, reduced glycolysis in certain resting or activated states, and abnormal relationships between immune-cell metabolism and cytokine levels. This supports the view that ME/CFS is not only a problem of fatigue or central nervous system function, but also an immunometabolic disorder in which immune-cell energy metabolism and cytokine signaling are tightly coupled.

Glucocorticoid Resistance and Failed Anti-Inflammatory Braking

A central mechanism is impaired anti-inflammatory braking. Glucocorticoid resistance in this context does not mean that cortisol is absent or that the glucocorticoid receptor cannot bind cortisol. It means that glucocorticoid receptor signaling may be dysregulated, blunted, inconsistent, poorly timed, or metabolically misdirected. The receptor may still be present and functional in some contexts, but the downstream anti-inflammatory response may not be reliable enough to restrain inflammation.

This distinction matters because glucocorticoid resistance does not protect against inflammatory reactivity. It may instead allow TNF-α, IL-1β, IL-6, NLRP3 inflammasome activation, mast-cell activation, histamine release, microglial activation, astrocyte inflammatory signaling, and LRRK2-related inflammatory responses to persist too easily. If the body cannot reliably apply the anti-inflammatory brake, ordinary stressors may produce disproportionate immune and metabolic consequences.

The newly merged material strengthens this section by showing how glucocorticoid receptor resistance can feed the HIF-1α–PKM2 metabolic-inflammatory loop. Normally, activated glucocorticoid receptor signaling suppresses NF-κB and limits pro-inflammatory cytokines. When GR/NR3C1 signaling is impaired, inflammatory cytokines remain elevated and may stabilize or upregulate HIF-1α even without classic hypoxia. HIF-1α then induces PKM2 and PDK4, sustaining aerobic glycolysis, inhibiting PDH, and driving lactate accumulation. Lactate

can further amplify NF-κB activity and promote histone lactylation, while the inflammatory environment continues to impair GR function. This creates a self-reinforcing cycle in which glucocorticoid resistance, inflammation, glycolysis, and lactate accumulation maintain one another.

Glucocorticoid Signaling in Astrocytes, MCT1, PDK4, PDH Inhibition, and Lactate Production

Kita-Shirakura et al. (2026) provide a strong mechanistic addition by showing that chronic glucocorticoid exposure can disrupt lactate homeostasis. In their mouse model, prolonged corticosterone exposure reduced cerebrovascular MCT1 expression and function, impaired lactate transport, elevated hippocampal lactate, suppressed hippocampal neurogenesis, and contributed to behavioral abnormalities. In the present hypothesis, this supports the view that dysregulated glucocorticoid signaling can actively impair the lactate shuttle. Chronic or ineffective glucocorticoid action may downregulate MCT1, contribute to extracellular lactate accumulation, stress hippocampal metabolism, reduce neurogenesis, and lower the threshold for cognitive, fear-related, and multi-system flares.

Glucocorticoid receptor signaling in astrocytes may also upregulate PDK4. PDK4 inhibits the pyruvate dehydrogenase complex, which normally allows pyruvate to enter mitochondrial oxidation through the TCA cycle. When PDH is inhibited, pyruvate is pushed away from mitochondrial oxidation and toward lactate production. In this model, dysregulated GR/NR3C1 signaling may therefore contribute to elevated lactate by shifting astrocyte metabolism away from efficient mitochondrial oxidation and toward glycolysis and lactate production.

Together, MCT1 downregulation and PDK4 upregulation create a double lactate burden: more lactate may be produced, while transport and clearance may be impaired. This provides a direct mechanistic bridge between chronic stress biology, glucocorticoid dysregulation, impaired astrocyte-neuron lactate shuttle function, hippocampal vulnerability, cognitive symptoms, and fear/autonomic instability.

NRF2 Impairment, Oxidative Stress, NLRP3, and Kynurenine Overdrive

NRF2 is a central protective pathway because it regulates antioxidant defense, detoxification enzymes, mitochondrial resilience, redox balance, and cellular recovery after oxidative stress. In this model, NRF2 responses may be impaired or overwhelmed by early toxicant exposure, chronic inflammation, reduced detoxification capacity, mitochondrial stress, mast-cell activation, pollutant exposure, and repeated flares.

If NRF2 is insufficient, the system may struggle to neutralize oxidative stress generated by inflammation, mitochondrial dysfunction, chemical exposure, glutamate excitotoxicity, histamine

reactions, infection, lactate-related metabolic strain, particulate exposure, diesel exhaust, smoke, pesticides, mold, construction dust, or poor water quality. Reduced CYP3A4/CYP3A5 activity may add to this vulnerability by decreasing the ability to process certain lipophilic compounds or medication exposures. This could help explain chemical sensitivity, smoke intolerance, medication sensitivity, and disproportionate procedure reactions.

Bahaa et al. (2026) support the clustering of oxidative stress, NLRP3 inflammasome activation, and kynurenine-pathway dysregulation. Their clinical biomarker findings in depression showed elevations in oxidative DNA damage markers, NLRP3, and kynurenine, supporting the idea that these pathways can operate as a measurable biological cluster. In this model, that same triad may contribute to neuroinflammation, excitotoxicity, depressive symptoms, cognitive dysfunction, PTSD-like features, and a lowered physiological stress threshold.

The SIRT1–PGC-1α–AMPK Axis and miRNA Regulation

The SIRT1–PGC-1α–AMPK axis adds an important layer to the model. SIRT1 is involved in inflammatory regulation, mitochondrial biogenesis, stress-response signaling, circadian rhythm, host defense, glucocorticoid sensitivity, and neuroprotection. PGC-1α helps regulate mitochondrial biogenesis, oxidative metabolism, neuroprotection, astrocyte maturation, oligodendrocyte myelination, microglial function, and lactate transport capacity. AMPK acts as an energy sensor that helps coordinate metabolic adaptation under stress.

If SIRT1 or PGC-1α activity is reduced by chronic inflammation, NAD+ depletion, norepinephrine deficiency, infection, oxidative stress, aging-related stress, viral persistence, or metabolic overload, the result may be impaired mitochondrial adaptation, weaker antioxidant defense, poorer glucocorticoid responsiveness, reduced MCT1-mediated lactate transport, and less effective resolution of inflammation. This is relevant because ME/CFS often involves impaired energy metabolism, poor recovery, abnormal responses to exertion, and difficulty restoring homeostasis after stress.

Kaczmarek (2023) adds a miRNA layer to this axis. Although circulating miRNA findings in ME/CFS may be heterogeneous, elevated miRNAs may converge on a shared cluster of target genes involved in exercise hyperemia, angiogenic adaptation to hypoxia, antioxidant defenses, TGF-β signaling, mitochondrial dynamics, and SIRT1-related regulation. Predicted SIRT1 downregulation may favor mitochondrial fragmentation, weakened antioxidant capacity, and circadian disruption. Many central elevated miRNAs may also be upregulated by herpesviruses, linking post-viral biology to epigenetic metabolic regulation. In the present model, reduced SIRT1 tone removes an important counter-regulatory brake on the HIF-1α–PKM2–lactate axis and inflammatory amplification.

Glucocorticoid Metabolic Rewiring, PDH, TCA Flux, and Itaconate

The model also incorporates glucocorticoid metabolic rewiring. Glucocorticoids can have anti-inflammatory effects partly by reprogramming macrophage mitochondrial metabolism. In this framework, glucocorticoids may increase PDH mitochondrial translocation, accelerate TCA cycle flux, and sustain production of the anti-inflammatory metabolite itaconate through IRG1. Itaconate helps restrain pro-inflammatory cytokines and NLRP3 activity.

If SIRT1–PGC-1α activity is impaired, this glucocorticoid-induced PDH–TCA–itaconate pathway may be blunted. This could mean that even if cortisol binds to its receptor, the downstream anti-inflammatory metabolic rewiring may not occur properly. If MCT1/MCT4 transport is also impaired, itaconate export and delivery to its immunomodulatory targets may be less effective. In this model, impaired SIRT1/PGC-1α function, altered MCT transport, and NR3C1 dysregulation converge to create a state in which glucocorticoids cannot reliably shut down inflammation.

This concept is important because it links glucocorticoid resistance to metabolism rather than treating it only as a hormone receptor problem. It suggests that impaired mitochondrial metabolism, PDH flux, TCA cycle function, MCT transport, and itaconate signaling may all contribute to persistent inflammation. It also connects to lactate elevation, because impaired PDH activity or impaired mitochondrial flux may push metabolism toward glycolysis and lactate production.

HIF-1α–PKM2–PDK4 and the Lactate Lock

The newly merged material adds a detailed metabolic-lock mechanism. Long-term stress, viral metabolic reprogramming, inflammatory signals, and hypoxic cues may converge on HIF-1α stabilization. Once activated, HIF-1α can upregulate PKM2 and PDK4. PKM2 supports high glycolytic flux and can participate in nuclear feedback that further stabilizes HIF-1α. PDK4 inhibits PDH, blocking pyruvate entry into the mitochondrial TCA cycle and shunting pyruvate toward lactate production.

When this state persists, aerobic glycolysis and lactate accumulation become maladaptive. Lactate may suppress antiviral interferon responses while synergizing with inflammatory signals to hyperactivate NF-κB. This creates an “antiviral failure–inflammatory amplification” loop in which lactate blunts viral clearance signals while increasing cytokine production. Chronic stress and glucocorticoid dysregulation may further induce PDK4 and impair counter-regulatory SIRT1–PGC-1α–AMPK and NRF2 pathways that would normally restore oxidative metabolism.

In a system already carrying genetic susceptibility, early environmental priming, mast-cell reactivity, and post-viral immune activation, this locked glycolytic-lactate state may lower the physiological stress threshold. It may fuel neuroimmune instability and contribute to post-exertional, inflammatory, sensory, autonomic, and multi-system flares.

Glycolysis, NLRP3, and Reciprocal Inflammatory Amplification

A 2026 review in the European Journal of Medical Research supports a reciprocal glycolysis–NLRP3 axis. Glycolytic enzymes, including hexokinases and PKM2, and metabolic intermediates such as lactate may actively orchestrate NLRP3 priming and activation. NLRP3 activation can drive pyroptosis, IL-1β release, IL-18 release, and inflammatory amplification. In turn, NLRP3-driven inflammation can reinforce a shift toward aerobic glycolysis.

This creates another self-reinforcing loop. HIF-1α and PKM2 promote glycolysis and lactate production. Lactate and glycolytic intermediates promote NLRP3 activation. NLRP3 increases IL-1β and inflammatory amplification. Cytokines further stabilize HIF-1α and reinforce glycolysis. In this model, the glycolysis–NLRP3 axis connects energy metabolism directly to neuroinflammation and mast-cell reactivity.

This is particularly relevant to PEM because exertion, stress, poor sleep, infection, dehydration, or sensory overload may all push cells toward glycolytic stress. If the system cannot return to oxidative metabolism efficiently, the inflammatory-glycolytic loop may remain active, leading to prolonged crashes.

Host-Derived Lactate, Interferon Suppression, and NF-κB Amplification

Tian et al. (2026) add a more detailed role for lactate in antiviral failure. Their work suggests that host-derived lactic acid can impair type-I interferon efficacy, promote viral immune evasion, and drive inflammatory amplification once viral infection is established. Mechanistically, lactate may suppress interferon activity through receptor-mediated SIRT1-related mechanisms while also synergizing with interferon signals to hyperactivate NF-κB and initiate cytokine storms.

In this model, lactate accumulation is not simply a passive marker of metabolic stress. It may actively contribute to incomplete resolution of post-viral inflammation. Elevated lactate may blunt antiviral defense while amplifying NF-κB-driven cytokine release. This creates a situation in which the body remains inflamed but ineffective at fully resolving viral or post-viral immune activation.

This mechanism helps explain why post-infectious states can become chronic. If lactate accumulation, impaired interferon signaling, NF-κB activation, HIF-1α stabilization, glucocorticoid resistance, and mast-cell reactivity reinforce one another, the system may remain stuck in a maladaptive inflammatory-metabolic state.

PKM2, Histone Lactylation, NF-κB, and CFS Progression

Sun et al. (2025) provide important support for a glycolysis–lactate–histone lactylation–NF-κB cascade in chronic fatigue-like states. In a murine CFS model, elevated PKM2 in hippocampal cells enhanced glycolysis and lactate accumulation, promoted H4K12 lactylation, activated NF-κB, increased pro-inflammatory cytokines such as IL-1β and TNF-α, and drove neuroinflammation and mitochondrial damage. PKM2 overexpression worsened cognitive performance and hippocampal pathology, while PKM2 knockdown improved these outcomes.

In this model, this strongly supports the HIF-1α–PKM2–PDK4–lactate lock as a driver of both metabolic failure and neuroimmune amplification. It also reinforces lactylation as a mechanism by which excess lactate may alter gene expression and sustain inflammation. Lactate is therefore not only an energy metabolite or a marker of poor clearance. It may become an epigenetic signal that changes inflammatory programming.

This is relevant to brain fog, hippocampal vulnerability, fear learning, memory disruption, altered salience, and severe flare states. It also helps connect metabolic dysfunction with neuroinflammation and cognitive symptoms.

Protein Lactylation, PTSD-Like Symptoms, and Cardiometabolic Stress

Kozlakidis et al. (2023) expand lactylation beyond CFS models. They describe protein lactylation as a lactate-driven post-translational modification of histone and non-histone proteins that may link metabolic stress, epigenetic regulation, inflammation, cellular senescence, PTSD-related physiology, and cardiovascular stress.

In this model, chronic lactate accumulation from impaired ANLS, HIF-1α–PKM2–PDK4 activation, mitochondrial strain, inflammation, and poor clearance could promote lactylation-related signaling. This could alter gene expression in immune cells, astrocytes, microglia, vascular cells, and threat-circuit neurons. If this occurs in circuits involved in fear learning, autonomic regulation, salience, or memory, it may contribute to persistent PTSD-like autonomic symptoms, altered threat processing, and stress intolerance.

This remains an emerging hypothesis. It is included because it provides a bridge between lactate accumulation, epigenetic change, inflammation, neuroimmune activation, and multi-system stress responses.

Astrocytes as Stress-Response Hubs and Exosome Signaling Cells

Astrocytes are increasingly central in this model because they serve as stress-response hubs. They regulate energy support, lactate shuttling, glutamate clearance, extracellular potassium, blood-brain barrier function, neurovascular coupling, glymphatic flow, antioxidant defense, synaptic plasticity, and immune signaling. They also release exosomes containing microRNAs

and other signaling molecules that can influence neurogenesis, inflammation, synaptic remodeling, and neuronal plasticity.

Stress can alter astrocyte exosomal miRNA cargo, potentially shifting the brain toward either adaptation or vulnerability. In this model, chronic stress, glucocorticoid dysregulation, inflammation, and impaired metabolic signaling may distort astrocyte exosome communication. This could reduce neurogenesis, worsen neuroinflammation, impair recovery after stress, reinforce maladaptive fear circuitry, and contribute to cognitive deficits.

Astrocytes are not passive support cells in this model. They may be active integrators of environmental stress, immune signals, metabolic state, circadian rhythm, hydration, mast-cell activity, gut-derived signals, and neuronal demand. If astrocytes become maladaptive, the entire network may lose flexibility.

Stress, Astrocytic Glycogen, Lactate Release, and Synaptic Plasticity

Another important mechanism is the idea that stress can gate an astrocytic energy reservoir. Astrocytes store glycogen and can mobilize it through glycogenolysis to produce lactate. In healthy contexts, astrocyte-derived lactate can support neurons and memory formation. Under chronic stress, inflammation, glucocorticoid dysregulation, or primed astrocyte states, this energy reservoir may become maladaptive.

Stress may trigger excessive astrocytic glycogenolysis and lactate release. Instead of supporting synaptic plasticity, excessive or poorly cleared lactate may impair long-term potentiation, disrupt hippocampal and cortical circuits, and contribute to cognitive dysfunction. In this model, dysregulated glucocorticoid signaling and inflammation may amplify this process. Stress may therefore produce excessive lactate release, extracellular accumulation, lactylation, oxidative stress, and impaired energy support.

This directly connects stress to PEM, brain fog, memory impairment, sensory overload, and lowered physiological threshold. It suggests that stress is not only an emotional experience. It may be a metabolic event in astrocytes that changes lactate handling and synaptic function.

The Glymphatic System, Deep Sleep, AQP4, and Clearance Failure

The glymphatic system is one of the most central parts of the updated hypothesis. Glymphatic clearance depends on deep sleep, cerebrospinal fluid flow, AQP4 polarization on astrocytic endfeet, vascular pulsatility, norepinephrine tone, hydration, and healthy astrocyte function. During restorative sleep, the brain has improved opportunity to clear lactate, inflammatory mediators, metabolic waste, ammonia-related burden, and potentially misfolded proteins.

In this hypothesis, glymphatic dysfunction may arise through several overlapping mechanisms. LRRK2/GBA-related vulnerability may affect lysosomal and protein-handling systems. Mast-cell and histamine activity may alter cerebrospinal fluid flow and the brain-dura interface. AQP4 dysregulation may impair astrocyte-mediated fluid movement. Norepinephrine deficiency may alter slow-wave vasomotion and reduce optimal glymphatic drainage. Dehydration may affect phosphorylated AQP4ex and water handling in the brain. Reduced deep sleep may further impair overnight clearance.

Together, these mechanisms could allow lactate, inflammatory mediators, ammonia-related burden, and metabolic waste to accumulate. This may contribute to brain fog, sensory overload, unrefreshing sleep, next-day PEM, neurological instability, and worsening autonomic symptoms. It may also explain why real-time tracking has repeatedly shown a relationship between sleep quality and next-day lactate or symptom burden.

Norepinephrine Deficiency, Irregular Noradrenergic Signaling, and Microglial Activation

Norepinephrine is another central node in the model. Norepinephrine helps regulate arousal, cortical state, vascular tone, slow-wave sleep physiology, mitochondrial biogenesis, attention, stress response, and astrocyte function. In this model, norepinephrine deficiency may impair slow-wave vasomotion and glymphatic drainage while also limiting mitochondrial biogenesis.

Norepinephrine–astrocyte signaling regulates cortical state homeostasis. If norepinephrine output is deficient, unstable, or poorly timed, astrocytes may not properly coordinate metabolic support, vascular coupling, glymphatic physiology, or neuronal state transitions. This could contribute to unrefreshing sleep, sudden “curtain closing” sleep attacks, impaired cognitive endurance, autonomic instability, and difficulty recovering after stress.

Irregular noradrenergic signaling may also drive microglial dysregulation. Phasic norepinephrine signaling may normally suppress microglial activation and support microglial surveillance. Chronic, irregular, or poorly timed norepinephrine signaling may instead contribute to hyperactivation and sustained inflammation. This means norepinephrine may not be simply “too low” or “too high.” It may be unstable. Baseline tone may be insufficient for stable arousal and recovery, while irregular surges may worsen autonomic alarm, fear states, microglial activation, and sleep disruption.

Melatonin, Astrocyte Mitochondrial Humanin, Orexin, and Nocturnal Flares

The astrocyte mitochondrial humanin–melatonergic axis remains an important part of the model. Humanin is a mitochondria-derived peptide that may show circadian variation and act as a signaling molecule linking astrocyte mitochondrial function, microglial inflammatory tone, and

neuronal melatonergic signaling. In this model, astrocytes are not only metabolic support cells. They may also help coordinate circadian mitochondrial signals that influence inflammation and melatonin-related neuronal function.

If early environmental priming, chronic inflammation, oxidative stress, SIRT1/PGC-1α dysfunction, or circadian disruption alters astrocyte mitochondrial humanin production, microglial activation may become less controlled and neuronal melatonergic signaling may weaken. This could reduce AQP4 polarization, impair glymphatic clearance, worsen sleep attacks, increase lactate accumulation after poor sleep, worsen cognitive symptoms, and contribute to a lowered physiological stress threshold.

Melatonin may promote sleep by inhibiting orexin neurons through MT1 receptor signaling, increasing NREM sleep and reducing wakefulness. Melatonin may also reduce neuroinflammation and microglial activation. It may support AQP4 polarization, glymphatic clearance, pain reduction, and inflammatory-marker modulation. In this hypothesis, melatonin decline, circadian disruption, and late-day blue light exposure may worsen orexin instability, AQP4 dysregulation, glymphatic impairment, microglial activation, nocturnal mast-cell activity, pain sensitivity, and next-day lactate burden.

The Broken Lactate Nexus in ME/CFS

The “Lactate Nexus” is a major part of this version. In healthy physiology, lactate is not merely a waste product. It can act as a beneficial signaling molecule linking physical activity, sleep, mitochondrial adaptation, brain energy support, hippocampal function, BDNF expression, and cognitive resilience.

In ME/CFS, this beneficial lactate signaling loop may become dysfunctional. If the astrocyte-neuron lactate shuttle is impaired, if MCT1/MCT2 transport is inefficient, if PGC-1α is reduced, if astrocytes are metabolically reprogrammed, if mitochondria are strained, or if deep sleep and glymphatic clearance are reduced, lactate may accumulate instead of supporting adaptation. Exercise-induced or stress-induced lactate may then contribute to extracellular accumulation, oxidative stress, inflammatory signaling, neuroimmune activation, and PEM rather than neuroprotective adaptation.

This may explain why conventional exercise can be harmful or ineffective in this case. Minimal activity, poor sleep, emotional stress, chemical exposure, gut irritation, dehydration, or procedures may raise lactate beyond the lowered threshold. Instead of producing improved conditioning, the lactate signal may become a marker and mediator of overload. This supports the importance of pacing, deep sleep optimization, hydration, mitochondrial support, and repair of underlying glial, shuttle, circadian, and clearance pathways rather than activity-based approaches that assume normal adaptation.

Mast Cells, HIF-1α, Microglia, IL-11, MMP-9, and Bidirectional Neuroimmune Amplification

The merged document adds a bidirectional mast-cell–HIF-1α relationship. Mast-cell activation under hypoxic or inflamed conditions may increase HIF-1α activity. HIF-1α then supports mast-cell survival, histamine production, mast-cell extracellular trap formation, IL-13 and IL-33 expression, and inflammatory tissue remodeling. In turn, mast-cell mediators may further stabilize HIF-1α in neighboring cells and contribute to local inflammatory tone.

This mast-cell–HIF-1α loop links mast-cell reactivity directly to glycolytic reprogramming, lactate accumulation, and chronic inflammatory stress. Under conditions of pollutant exposure, post-viral inflammation, or chronic stress, this loop may reinforce histamine-driven reactivity, cytokine release, tissue sensitivity, and metabolic dysfunction.

The model also includes bidirectional mast-cell–microglia communication. Mast cells and microglia can influence each other through cytokines, histamine, tryptase, chemokines, inflammatory mediators, and possibly signaling across the brain-dura interface and blood-brain barrier. In a primed system, activated mast cells may stimulate microglia, and activated microglia may further activate mast cells.

Elevated IL-11 and MMP-9 are also relevant to this mast-cell-linked pattern. MMP-9 may contribute to blood-brain barrier disruption, tissue remodeling, and inflammatory permeability changes. IL-11 may participate in inflammatory, fibrotic, or tissue-remodeling processes. In this model, elevations in these pathways could support increased mediator release, barrier vulnerability, neuroinflammatory amplification, and mast-cell-related tissue sensitivity.

Substance P–MrgprX2 Neuroimmune Mast-Cell Activation

The newly merged material adds the Substance P–MrgprX2 axis as a concrete non-IgE mast-cell activation pathway. Sensory neurons can release Substance P, which directly engages MrgprX2 on mast cells. This can trigger rapid degranulation, histamine release, mediator release, epithelial barrier disruption, and inflammatory amplification independently of classic IgE/FcεRI signaling.

This pathway is important because it links stress, sensory triggers, pain, itch, chemical sensitivity, and environmental irritation to mast-cell activation. It helps explain how neural signals can drive mast-cell symptoms even when traditional allergy mechanisms do not fully account for reactions. Sustained Substance P–MrgprX2 activation may establish positive neuroimmune feedback loops and contribute to central sensitization.

In the present model, this axis helps connect sensory overload, environmental triggers, stress, itching, burning, flushing, migraines, and autonomic symptoms. It also helps explain why mast-cell symptoms may occur during neurological or PTSD-like states, because sensory neurons, autonomic arousal, and mast cells may be coupled through neuroimmune signaling.

Central IL-1β-Encoding Neurons and Stress-Induced Inflammation

Hashimoto et al. (2026) add a direct neural substrate for bidirectional stress–inflammation coupling. Their work demonstrates that specific central neurons can encode IL-1β signals and drive systemic inflammatory and autonomic responses. CRH-expressing neurons in the bed nucleus of the stria terminalis can respond to IL-1β and generate downstream effects involving circulating IL-6, corticosterone, tachycardia, and autonomic activation through stress-related brainstem pathways.

This is important because the same neurons may also be activated by restraint stress and generate similar physiological effects. In this model, stress and inflammation are therefore not separate categories. Inflammatory cytokines can activate stress circuits, and stress circuits can generate inflammatory and autonomic outputs.

This mechanism helps explain why psychological stress, physical inflammation, infection, mast-cell flares, and autonomic episodes may feel interchangeable or fused. IL-1β-driven neural circuits may lower the threshold for tachycardia, fear states, inflammatory amplification, and HPA-axis activation. This strengthens the model's interpretation of PTSD-like symptoms as physiological stress-inflammation coupling rather than purely psychological reactivity.

Gut Dysbiosis, Butyrate, AhR Signaling, and Brain–Astrocyte Effects

The gut-brain-immune axis remains important because gut irritation, dysbiosis, increased permeability, bacterial translocation, microbial extracellular vesicles, or mast-cell activation in the gut can amplify systemic cytokines and neuroimmune signaling. Dysbiosis is a recurring and often severe symptom pattern, frequently intensifying with stress and improving with probiotics or gut-supportive strategies.

Reduced populations of butyrate-producing gut bacteria may impair local AhR activation in the intestine. Butyrate is a short-chain fatty acid produced by commensal bacteria and can influence histone deacetylase activity, immune regulation, gut barrier function, and inflammatory tone. In this model, reduced butyrate and impaired AhR signaling may weaken intestinal barrier integrity, reduce regulatory immune responses, and increase systemic inflammation.

Signals from the dysbiotic gut may reach the central nervous system through circulating metabolites, immune mediators, microbial extracellular vesicles, or vagal pathways. In the brain, AhR is expressed in astrocytes and may influence astrocytic inflammatory tone, metabolism, and possibly AQP4 polarization. If AhR signaling is reduced, astrocytes may become more sensitive to inflammatory stimuli and less able to resolve inflammation. This could worsen neuroinflammation, AQP4 dysregulation, lactate mishandling, glymphatic impairment, and lowered stress threshold.

Miller and Johnson (2026) add dietary amino acids as a possible barrier-restoration support. Their systems-biology modeling work suggests that glutamine, arginine, and tryptophan may support tight-junction protein synthesis and assembly through metabolic and signaling pathways involving mTOR and NF-κB cross-talk. In this model, barrier integrity is an upstream node because gut leakiness can increase systemic inflammation, mast-cell activation, and neuroimmune signaling.

Probiotics, Lactate-Related Genes, Fatigue, and Gut-Metabolic Coupling

Song et al. (2026) add probiotic effects on metabolic stress, fatigue, and lactate-related genes. In a mouse model combining forced swimming stress and LPS-induced inflammation, a probiotic formula reduced oxidative and inflammatory markers, improved endurance and pain sensitivity, restored expression of Hcar1 and Slc16a1, and shifted the gut microbiota. Hcar1 is related to lactate sensing, while Slc16a1 encodes MCT1, a major lactate transporter.

In this model, these findings reinforce the interconnected gut–metabolic–lactate node. Gut microbiota may influence inflammation, oxidative stress, lactate sensing, lactate transport, fatigue, pain sensitivity, and resilience to metabolic stress. This supports the idea that gut-directed interventions may influence systemic energy regulation and neuroimmune stability, not merely digestion.

This does not mean any specific probiotic is guaranteed to help. It means the gut-lactate-immune connection is biologically plausible and relevant to the broader framework. Probiotics, butyrate-supportive nutrition, gut barrier support, and medical-food-type interventions may be reasonable clinician-discussion topics if tolerated.

Orexin, GLP-1, Post-Viral Syndromes, and Metabolic Regulation

The model also includes regulatory cycles between orexin and GLP-1 in post-viral syndromes such as ME/CFS and Long COVID. Orexin promotes arousal, wakefulness, stress responses, feeding-related signaling, and autonomic activation. GLP-1 modulates metabolism, inflammation, neuroprotection, glucose handling, and possibly brain circuits involved in anxiety and threat processing. Viral triggers may desynchronize these regulatory cycles, producing unstable wakefulness, metabolic dysregulation, autonomic symptoms, and neurological flares.

In this model, orexin-GLP-1 imbalance may contribute to sleep attacks, fear episodes, energy crashes, unstable arousal, and poor metabolic recovery. GLP-1 receptor agonist pathways are therefore included as a possible clinician-guided research area. Their relevance would not be limited to glucose regulation. They may also affect inflammation, astrocyte-neuron lactate coupling, gut-brain signaling, and amygdala-hippocampal modulation of PTSD-like anxiety. This

is not a recommendation to use GLP-1 agents, but it identifies a pathway worth discussing with clinicians if appropriate.

Pro-Inflammatory Cytokines, PTSD-Like Symptoms, and Serotonin–Kynurenine Pathway Alterations

Ogłodek (2026) strengthens the PTSD-like portion of the model by emphasizing pro-inflammatory cytokine processing as a central mechanism in PTSD pathophysiology. In this framework, cytokines are not secondary noise. They may actively shape threat processing, arousal, fear extinction, autonomic tone, and neuroinflammation.

This aligns with the hypothesis that abrupt fear/autonomic switches, hypervigilance, and neurological features may be driven by physiological dysregulation within an immune-metabolic-neuroinflammatory network. Elevated or dysregulated TNF-α, IL-1β, IL-6, NLRP3 inflammasome activity, and microglial activation may lower the threshold for fear/autonomic episodes and sustain threat-circuit instability even when there is no obvious psychological trigger.

Peripheral serotonin–kynurenine pathway alterations are also relevant. Inflammation can shunt tryptophan metabolism away from serotonin and toward kynurenine metabolites. Some kynurenine metabolites may influence excitotoxicity, glutamate signaling, microglial activation, mood, cognition, and threat-circuit activity. In this model, chronic inflammation and mast-cell activation may drive kynurenine overdrive, contributing to PTSD-like symptoms, brain fog, sensory sensitivity, and neurological instability.

Dopamine Prediction Error, GRIN2A/NMDA Signaling, and Movement Instability

Dopamine prediction-error signaling is relevant because dopamine responses to unexpected aversive outcomes can drive the return of extinguished fear. In this model, early priming from TCE, smoke, viral illness, chronic inflammation, and chemical sensitivity may create strong aversive associations with chemicals, internal body sensations, or environmental stimuli. If dopamine prediction-error circuits are dysregulated, the brain may have difficulty updating safety signals after repeated exposures.

GRIN2A is relevant because NMDA receptor signaling affects glutamate handling, calcium dynamics, salience, prediction error, fear learning, feedback processing, and motor stability. GRIN2A-related NMDA vulnerability may interact with impaired astrocytic glutamate clearance, lactate stress, microglial activation, SIRT1 impairment, and LRRK2/GBA-related pathways. In severe flares, this interaction may increase vulnerability to circuit instability.

Ataxia-like “wobbles,” movement instability, reduced movement confidence, sensory overload, visual trails, aberrant salience, and rare neuropsychiatric symptoms may reflect transient

dysfunction in dopamine/NMDA motor and salience circuits. This does not mean Parkinson's disease is confirmed. It is included as a cautious motor-circuit vulnerability hypothesis.

LRRK2/GBA, Microglia, Astrocytes, and Dopaminergic Vulnerability

LRRK2 and GBA-related vulnerability are included cautiously as possible modifiers of immune, glial, lysosomal, and dopaminergic stress. LRRK2 is involved in immune signaling, inflammatory regulation, autophagy, lysosomal function, mitochondrial stress, vesicle trafficking, microglial activity, and astrocyte function. If LRRK2 G2019S is clinically confirmed and relevant to this background, it may interact with chronic mast-cell-driven TNF-α/IL-1β signaling, oxidative stress, infection, and early environmental priming to amplify inflammatory vulnerability.

LRRK2-related pathways may also affect astrocytic glutamate transporter trafficking, including EAAT2, which could increase synaptic glutamate accumulation and excitotoxic risk. LRRK2 may also alter dopamine D2 receptor localization in astrocytes, impairing neuronal support. If astrocytes cannot properly support dopamine circuits, the brain may become more vulnerable to movement instability, salience disruption, and stress-related dopaminergic dysfunction.

GBA-related pathways may be relevant because GBA biology is connected to lysosomal function, protein handling, and Parkinson's-associated vulnerability. In this model, these pathways may increase dopaminergic sensitivity during severe inflammatory-metabolic flares without implying a Parkinson's diagnosis. The point is not that Parkinson's disease is confirmed. The point is that LRRK2/GBA biology may overlap with immune, lysosomal, mitochondrial, microglial, and dopaminergic mechanisms that could become relevant during severe flares.

Sensory Neuropathy, Schwann Cells, Oligodendrocytes, Myelin, and B12/Folate

The updated model also includes sensory neuropathy, Schwann cell repair, oligodendrocyte function, myelin biology, and fear-memory reinforcement. Clinician-noted sensory neuropathy/hypoesthesia suggests that peripheral sensory pathways may be involved in addition to central neuroinflammation. Chronic inflammation, mitochondrial stress, ER stress, impaired methylation, B12/folate insufficiency, oxidative stress, immune activation, and metabolic strain may affect nerve function or repair capacity.

B12 is relevant because methylcobalamin and related B12 pathways may support Schwann cell differentiation, nerve repair, myelin maintenance, and neuroprotection. Folate is relevant because it supports methylation and homocysteine regulation. Together, B12 and folate may influence myelin integrity, nerve repair, dopaminergic resilience, glucocorticoid receptor function, and ER-stress-related pathways.

Oligodendrocyte energy metabolism and remyelination are also relevant because myelin maintenance is energetically demanding and may be impaired by mitochondrial dysfunction, inflammation, or glial metabolic stress. PTSD-like persistence may involve activity-dependent oligodendrogenesis and myelin remodeling in fear-memory circuits. This means fear/autonomic states may become biologically reinforced through changes in circuit conduction and insulation, not only through psychological memory.

Clinical Manifestations and Threshold-Crossing

The clinical manifestations can be understood as abrupt threshold-crossing events. Symptoms can include PEM, MCAS-like reactions, sickness behavior, profound fatigue, brain fog, reduced motivation, fear episodes, ataxia-like “wobbles,” movement instability, photophobia, visual trails, sleep attacks, shivering, temperature dysregulation, burning sensations, gut-triggered symptoms, histamine reactions, altered states, amnesia, and rare neuropsychiatric symptoms during extreme crashes.

The 1983 viral pneumonia with heavy secondhand smoke exposure during stress appears to have been the major tipping point into chronic illness. Medical procedures, environmental exposures, gut irritation, sleep disruption, chemical exposure, stress, sensory overload, dehydration, construction dust, mold, pesticides, poor water quality, air pollution, and infections can still activate the same network now. The model helps explain why flares may feel automatic, sudden, and multi-system rather than gradual or isolated.

Therapeutic and Behavioral Strategy Framework

The therapeutic and behavioral strategy section is framed as clinician-discussion topics rather than treatment instructions. Because of medication sensitivity, sedation risk, bleeding risk, kidney function considerations, interactions, paradoxical reactions, and individual genetics, all interventions should be reviewed with a healthcare provider.

Deep sleep optimization remains the cornerstone because sleep may support glymphatic clearance, lactate clearance, inflammatory mediator clearance, autonomic stability, orexin regulation, melatonin rhythm, mitochondrial recovery, pain regulation, and next-day resilience. Strict avoidance of blue light late in the day is included because preserving melatonin production may reduce circadian disruption, improve sleep architecture, stabilize orexin, support AQP4 polarization, and reduce microglial activation.

Pacing and stress management remain essential because they reduce threshold crossing. This includes limiting physical, cognitive, emotional, sensory, chemical, orthostatic, circadian, and procedural load. The model supports pacing not as avoidance for its own sake, but as a strategy to prevent lactate accumulation, immune activation, mast-cell flares, and PEM.

Mast-cell stabilization and histamine reduction may reduce cytokine amplification and lower the risk of flares. Strategies in this category would need to be individualized and clinician-guided, especially because of medication sensitivity.

NRF2 and antioxidant support, including resveratrol, quercetin, sulforaphane, omega-3 fatty acids, curcumin or related polyphenols, and possibly rutin where appropriate and tolerated, may support antioxidant defenses, SIRT1/PGC-1α pathways, mast-cell stabilization, and astrocytic resilience. Melatonin supplementation may be relevant because it may support sleep architecture, inhibit orexin activity through MT1-mediated mechanisms, support AQP4 polarization and glymphatic restoration, reduce nocturnal mast-cell activation, reduce neuroinflammation, and possibly help with pain or inflammatory markers.

Hydration and electrolyte management are explicit targets because dehydration may affect AQP4 polarization, glymphatic function, orthostatic symptoms, kidney-brain water handling, and lactate burden. Gut barrier and microbiome support may be relevant because gut-derived inflammatory signals can amplify mast-cell activation and systemic cytokine burden. Vitamins A, C, D, and E may support barrier function and antioxidant defense if clinically appropriate. B12 and folate may be relevant for methylation, myelin maintenance, homocysteine regulation, dopaminergic resilience, glucocorticoid receptor support, nerve repair, and ER-stress-related pathways. Glutamine, arginine, tryptophan, probiotics, butyrate-supportive strategies, and other gut-barrier approaches may also be clinician-discussion topics if tolerated.

Potential exploration of GLP-1 receptor agonist pathways, LRRK2 kinase modulation, fine-tuned glucocorticoid receptor modulation, dual orexin receptor antagonist concepts, and mitochondria-targeted antioxidants should remain clinician-guided and cautious. Procedure planning is also a high-leverage target because medical procedures can trigger combined mast-cell, metabolic, autonomic, and neuroimmune flares. Hydration, medication tolerance review, sedation planning, mast-cell stabilization if appropriate, minimizing sensory stress, and post-procedure recovery planning may reduce risk.

Neurological monitoring is important because persistent tremor, rigidity, worsening gait instability, progressive motor change, worsening sensory neuropathy, worsening hypoesthesia, worsening visual symptoms, worsening syncope, or progressive movement symptoms should be evaluated clinically rather than assumed to be part of ME/CFS or MCAS.

Overall Summary

Overall, this research summary frames ME/CFS, MCAS-like symptoms, PTSD-like autonomic/fear episodes, neurological symptoms, sensory neuropathy/hypoesthesia, chemical sensitivity, environmental sensitivity, gut sensitivity, sleep disruption, and metabolic instability as outputs of one unstable immune-metabolic-neuroinflammatory network shaped by gene–environment interactions. The model helps explain why symptoms feel fused, why flares switch on abruptly, why deep sleep and pacing are critical, why environmental exposures and genetics may matter, why mast cells and metabolism are central, why lactate tracking may

reflect illness burden, why medical procedures can trigger severe multi-day flares, why air pollution and weather changes may worsen symptoms, why threat-circuit symptoms may arise from physiological dysregulation rather than purely psychological triggers, and why glial, glymphatic, mitochondrial, circadian, gut-brain, and immune stabilization may all be relevant.

The core proposed pattern is genetic susceptibility plus early environmental exposure plus developmental stress plus impaired NR3C1/glucocorticoid and NRF2 regulation plus SIRT1/PGC-1α/AMPK impairment plus mast-cell and histamine activation plus AhR dysregulation plus kynurenine pathway overdrive plus glymphatic impairment plus AQP4 dysregulation plus HIF-1α–PKM2–PDK4 lactate locking plus lactate-driven NLRP3 activation plus astrocytic metabolic dysfunction plus impaired lactate/glutamate handling plus orexin instability plus noradrenergic dysregulation plus microglial activation plus dopamine prediction-error dysfunction plus NMDA/GRIN2A vulnerability plus possible LRRK2/GBA-related vulnerability plus lactylation-related signaling plus gut dysbiosis and barrier disruption. Together, these pathways may lower the threshold for PEM, MCAS-like flares, fear episodes, neurological instability, sensory neuropathy symptoms, movement symptoms, metabolic decompensation, and severe crashes.

This model remains provisional, but it organizes the most plausible pathways into a coherent framework. It may help guide clinical discussion, monitoring priorities, trigger avoidance, sleep optimization, pacing, hydration planning, procedure planning, environmental-exposure reduction, gut support, neurological follow-up, metabolic evaluation during severe flares, and targeted stabilization strategies.